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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/601,644	GARIEPY ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya, Ph.D.	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-18,20,24,25,27-29,32,33,37-41 and 43* is/are pending in the application.

4a) Of the above claim(s) *17,24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-16,18,20,27-29,32,33,37-41 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-7, 9-18, 20, 24, 25, 27-29, 32, 33, 37-41 and 43 are pending. Claims 17, 24, and 25, are withdrawn from consideration. Claims 1-7, 9-16, 18, 20, 27-29, 32, 33, 37-41 and 43 are examined.

Election/Restrictions

2. Applicant argues that the restriction requirement as to claims 17, 24 and 25 should be withdrawn under the principles of unity of invention because claim 1 is now allowable over the prior art and because claim 32 has the same special technical feature as claim 1.

Applicant's arguments have been considered but are not considered persuasive. Claims 1 and 32 are not allowable, as they are rejected under 35 USC 112, first paragraph.

Priority

3. This application, 09/601,644, is the national stage under 35 U.S.C. 371, of PCT/CA98/01137, filed 12/08/1998. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy of Canadian priority document 2,222,993, filed on Feb. 4, 1998, appears in the instant application papers, and in PCT/CA98/01137, filed 12/08/1998.

Withdrawn Objections and Rejections

4. The following rejections are withdrawn in view of applicant's amendments to the claims and arguments:

5. Claims 15, 20, and 27-29 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

6. Claims 24, 25, 32 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 112, First Paragraph

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 1-7, 9-16, 18, 20, 27-29, 32, 33, 37-41 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for lack of written description.

This rejection is maintained for the reasons of record as set forth in the previous Office action in the rejection of claims 1-16, 42 and 43. The rejection is copied below for the convenience of the reader. The new grounds of rejection are in response to the examination of previously withdrawn claims.

The claims are drawn to a method for making a cytotoxic mutant protein having a different receptor-binding specificity than the wild type protein, comprising incorporating mutations into DNA encoding the binding domain of a heteromeric protein toxin to produce variant forms of the heteromeric protein toxin, generating a library of clones to produce variant forms of the heteromeric protein toxin, screening against a population of screening cells and selecting a cytotoxic mutant protein that inhibits or kills said population of screening cells to a greater extent than wild-type cytotoxic mutant protein.

Vas-Cath Inc. v. Mahurkar, 19 USPQ 2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See Vas-Cath at page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 116). The claimed genus of cytotoxic proteins is broad and includes species named in the specification and claimed, such as Shiga toxin, Shiga-like toxins, ricin, abrin, gelonin, crotin, pokeweed antiviral protein, saporin, momordin, modeccin, sarcin, diphtheria toxin and Psudomonas aeruginosa exotonin A, as well as other species not described, such as snake, lizard, spider and insect venoms (see, e.g., US Patent No. 6,833,131 at col. 1, lines 10-35; US Publication No. 2002/0161203 A1 at para [0005], [0190]). The specification provides specific embodiments, working or otherwise, only for Shiga-toxin and Shiga-like toxins. In the Specification, at Example 4, pp. 22-23, the method used for producing a cytotoxic mutant protein having a different receptor-binding specificity than the wild type protein appears to rely on using the CAMA-I cell line, because it lacks the CD77 marker that is the receptor for Shiga toxin and Shiga-like toxin (p. 12, lines 16-19). The specification does not disclose cell lines that similarly lack the receptors for the other heteromeric protein toxins that constitute the genus. The examiner respectfully submits that the specification does not provide a representative number of species to show possession over the entire genus claimed. It is noted that the examined claims do not require that the screening cell line lack the receptor recognized by the wild-type toxin.

The specification at p. 25, lines 25-29, states that the "B subunit variants may thus bind to a spectrum of molecular entities such as proteins, peptides, nucleic acids or even organic moieties rather than to sugars or glycolipids (such as CD77)." However, in regard to the embodied species of Shiga-toxin, the specification does not describe what different receptor the mutated B subunit now has specificity for and describes no assays, actual or prophetic, to demonstrate positively that the mutated toxins now have specificity for a different receptor, as claimed. Also, the specification does not disclose that the mutated B subunits do not bind to the CD77; rather that the mutated toxin kills CAMA-1 cells, which the specification teaches lacks CD77, and SKBR-3 cells, which the specification teaches expresses CD77 (Specification at p. 22, lines 4-14). Given the unpredictability of the arts of biology and of mutation, particularly in changing the target of a protein ligand, extrapolation from cytotoxicity data (see Specification at Example 4, pp. 22-23) that the mutated Shiga toxin B subunit has a different receptor-binding specificity is uncertain. The Office does not have the facilities and resources to provide the factual evidence needed in order to determine that the cytotoxic mutant protein has a different receptor-binding specificity than the wild type protein. It is respectfully submitted that the practitioner would not be

reasonably apprised that the applicant was in possession of the claimed invention, in regard to the particular species of Shiga toxin or Shiga-like toxin.

Vas-Cath Inc. v. Mahurkar, 19 USPQ 2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See Vas-Cath at page 1117). See, also, Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 § 112 is severable from its enablement provision.

Response to Arguments, Mailed 2/27/2006

The applicant argues that amending the claims to recite that the heteromeric protein toxins are ribosome-inactivating protein (RIP) overcomes the instant written description because RIPs are described in the specification and include the Shiga and Shiga-like toxins. The applicant argues that the two breast cancer cell lines described in the specification is representative of the genus of screening cells because the particular cell type used in the claimed method is not critical, provided the combination of toxin and cell type are such that a selection can be made based on an observed increase in toxicity. Applicant argues that an important benefit of the present invention is that it does not require any prior or subsequent knowledge of the specific nature of the receptor. Applicant states:

> The screening techniques identifies, via observed toxicity, the mutation that works in combination with some receptor on the screening cells, and neither the nature of the receptor nor the nature of the mutation needs to be known. While it may be interesting to know the type of receptor a new toxin binds to, this is not a reason to say that there is no written description of the invention as claimed.

Reply at p. 11, para 2.

Applicant's arguments entered, 11/21/2005, have been fully considered but they are not persuasive.

The specification does not provide a representative number of species to show possession over the entire genus of RIP claimed. Heteromeric RIP, as claimed, appear to represent type 2 RIP. The genus of type 2 RIPs include certain plant toxins, such as the lectin ricin, and bacterial toxins, including Shiga toxin and Shiga-like toxin, produced by enterohemorrhagic strains of Escherichia coli, as well as other toxins (see Hartley et al., Biochimica et Biophysica Acta (2004), 1701, pp. 1-14, and especially p. 2, para 3 and Table 1). The specification as filed includes some of these type 2 RIPs, such as ricin, abrin, momordin, shiga toxin and shiga-like toxin, but does not disclose others, such as volkensin, viscumin, ebulin b, SNAI, SNAV, or SNAIf.

The claims are drawn to selecting mutant proteins with a different binding specificity than the wild type binding protein. Applicant bases this element on the use of the CAMA-1 cell line, which appears to lack the CD77 glycolipid, to which the Shiga toxin and Shiga-like toxin bind, (as taught by the instant specification). It appears that applicant reasons that because the CAMA-1 cell line lacks the CD77 receptor, the mutated toxins must act by having a different receptor binding specificity, i.e., binding to a different receptor. However, the specification does not describe species of cell lines that lack the receptors for different species of the genus of RIPs, other than the CAMA-1 cell line, which is specific for Shiga toxin or Shiga like toxin. For example, there are no described cell lines that are resistant to volkensin, viscumin, ebulin b, SNAI, SNAV, or SNAIf.

The practitioner would not envision that the applicant had process of mutant proteins that have different receptor specificity. Applicant has not identified what receptor the mutated Shiga toxin or Shiga-like toxin binds to and therefore, the specification cannot describe it. Roberts et al., Mini Reviews in Medicinal Chemistry (2004) Vol. 4, pp. 505-512, throughout the publication, and e.g., at p. 507, para 2, teach that the RIP ricin, is taken into the cell by endocytosis after binding galactosides on the mammalian

cell surface. Roberts et al. states "[t]he precise endocytic route may be influenced by the nature of the surface molecule to which the toxin has bound, and since ricin promiscuously binds to many different surface glycoproteins, it isn't perhaps surprising to find that it can enter by both clathrin-depenent and clathrin-independent endocytosis." Thus the RIP and its mutant protein may have common specificity to one or more of several different receptors. Perhaps a mutant RIP continues to have the same receptor binding specificity, but other pathways are affected or different.

The publication of Battelli, Mini Reviews in Medicinal Chemistry (2004) Vol. 4, pp. 513-521, throughout the publication, and e.g., at p. 513, bridging paragraph and p. 513, para 2, teaches that "[c]omparing the cytotoxicity of various type 2 RIP for a cell line and, conversely, the different sensitivity of various cell lines to the same toxin, it appeared clear that the interaction between cells and RIP was more complicated that it was predictable on the basis of the molecular structure." Battelli states that "t]he correlation between RIP structure and cytotoxicity had become even less linear when a new category of type 2 RIP emerged, which, in spite of the presence of the lectinic chain, have a low toxicity, similar to that of type 1 RIP (Table 1). . . . For instance, the lower cytotoxicity of nigrin b compared with ricin has been at least in part explained by a higher degradation of nigrin b by cells, with a resulting lower concentration remaining inside the cells, and by the different intracellular pathways followed by the two lectins". Thus it is clear that the genus of RIPs is heterogeneous, unpredictable, and complicated in the mechanism of action. Therefore, one of skill in the art would not envision that the applicant had possession of the invention as now claimed.

Furthermore, in regard to newly examined claims, drawn to methods of making probes and mendicants, the specification does not provide guidance and direction for detecting or treating disease, *in vivo*.

In regard to said methods of making mendicants, it is respectfully noted that the instant claims read upon vectors for gene therapy, which is an unpredictable art. In particular, sufficient delivery to and expression in target tissues is not predictable. Kaneda, "Gene Therapy: A Battle Against Biological Barriers", Current Molecular Medicine 2001, Vol. 1, pp. 493-499, throughout the publication and abstract, teaches that successful gene therapy is dependent on the development of an effective gene delivery system. Kaneda teaches that gene therapy continues to stymied by problems in targeting, permanence and quantity of expression of the gene in question, immunogenicity, etc. Kaneda notes that various gene delivery systems, including adenovirus systems, have well known limitations that have prevented safe and successful methods of gene therapy.

Response to Arguments, mailed 11/20/2006

Applicant argues that improperly, the examiner has not looked at the "particular invention" as claimed to determine if written description exists, (citing *Capon v. Eshar*, 76 USPQ2d 1078 (Fed. Cir. 2005)). Applicant argues that because the specification disclosed the generic name of ribosome inactivating proteins and a number of examples, a person skilled in the art would know, unequivocally, that applicant understood the invention to include toxins within this genus at the time the invention was filed. Applicant argues that the examiner's allegation that the lack of additional cell lines suitable for use with toxins other than Shiga or Shiga-like toxin (i.e., the CAMA-1 cell line), focuses too narrowly on the elements and not on the claimed invention because the method, (whose purpose is to allow development of binding portions) can be applied to cells different from CAMA-1. Applicant argues that the alleged lack of possession of mutant proteins that have different receptor binding specificity is not relevant, as applicant are claiming a method of identifying proteins, (directing the examiner's attention to Examples 10 and 18 of the Examination Guidelines on Written Description (uspto.gov/web/menu/written.pdf)). Applicant argues that others may use the claimed method, including the key screening step, in the future to make additional proteins not specifically disclosed, and that to deny patent protection to the applicant against such use is improper, (directing the examiner's attention to *In re Fuetterer*, 319 F.2d 259, 138 USPQ 217 (CCPA 1963).

Applicant's arguments entered, 6/27/2006, have been fully considered but they are not persuasive.

The specification does not provide description for the full scope of making cytotoxic mutant proteins for any heteromeric ribosome inactivating protein toxin because the specification does not describe the nucleic acid sequences for ribosome inactivating proteins and does not provide cell lines that are insensitive to ribosome inactivating protein toxins, except for Shiga toxin and Shiga-like toxin. Furthermore, the specification does not point to where in the art, at the time of filing (1998), these elements could be found. The specification as filed does not describe that the sequences for the heteromeric ribosome inactivating proteins were known; and the specification does not describe cell lines insensitive to the heteromeric ribosome inactivating proteins, other than CAMA-1, (which is insensitive to Shiga toxin and Shiga-like toxin). The examiner submits that one of skill in the art would not know what cells to substitute for CAMA-1. Absent evidence to the contrary, these gene sequences and cell lines would have to be created *de novo*, before the claimed method could be practiced in its full scope. Therefore, one of skill in the art would not envision that applicant had possession of the claimed method drawn to making a cytotoxic mutant protein that is any heteromeric ribosome inactivating protein.

The nature of the receptor is relevant to enablement of the claimed invention, at least because the amended claim states that the mutated proteins have a "receptor-binding specificity for a receptor that is different from the receptor to which the wild type protein has receptor binding specificity". Without recognition of the nature of the receptor to which the mutated protein binds, one of skill in the art would not be reasonably apprised that the receptor was different, as required by the claims. It is

respectfully noted that one of skill in the art would appreciate that insensitivity to a toxin might result from a variety of reasons, such as amplification of the gene of a target protein or an enhanced toxin efflux mechanism in the insensitive cell, (*compare*, D'Andrea, U.S. 2003/0188326, at para 71, discussing various possible causes for drug resistance).

In regard to conformance with Examples 10 of the Examination Guidelines on Written Description, the examiner respectfully notes that Example 10 contemplates claims drawn to a method for isolating polynucleotide comprising hybridizing a specific sequence, as denoted by a sequence identifier, which is different from the instant claims, which do not provide nucleotide sequences for the genus of ribosome inactivating proteins. Furthermore, the examiner respectfully submits that the specification does not indicate where to find sequences of that genus in the prior art.

In regard to Example 18, the examiner respectfully notes that Example 18 contemplates that the art teaches that a particular nucleic acid is not essential to the claimed method of producing a protein of interest in *Neurospora*, which is a different circumstance from the instant claims, because each of the different heteromeric ribosome inactivating protein mutants would require a corresponding cell line that was insensitive to that heteromeric ribosome inactivating protein. Absent evidence to the contrary, one of skill the art would not know whether such insensitive cell lines exist, except for the single example of the CAMA-1 cell line.

In regard to applicant's argument that others may use the claimed method, including the key screening step, in the future to make additional proteins not

specifically disclosed, and that deny patent protection to the applicant against such use is improper (citing *In re Fuetterer*), the examiner respectfully submits that the unlike the different inorganic salts of *In re Fuetterer*, which served merely to maintain carbohydrates or proteins in a colloidal suspension simply by virtue of being a salt, each individual and different heteromeric ribosome inactivating protein and its corresponding insensitive cell line, cannot stand in the place of the other heteromeric ribosome inactivating proteins and their corresponding insensitive cell line. That is to say, having the CAMA-1 cell line, which is insensitive to Shiga toxin and Shiga-like toxin, does not convey possession for mutants other ribosome inactivating proteins which have specificity for a receptor that is different from the receptor to which the wild type protein has receptor binding specificity, because of unpredictability of the molecular biology of ribosomal inactivating proteins, as taught by Battelli, (of record).

Response to Arguments

Applicant argues that recitations of known nucleic acid/amino acid sequences are not required for written description. Applicant's point to exemplary documents in Exhibit A. Applicant argues that the claimed invention is generally applicable, and so no creation of a cell line is required, just the existence of cells that are of interest. Applicant argues that what is claimed is a method for finding of combinations of ribosome inactivating proteins (RIP) and insensitive cell lines.

Applicant's arguments, entered 4/9/2007, have been fully considered but they are not persuasive. The examiner respectfully submits that the exemplary documents

provided do not indicate that representative nucleic acid/amino acid sequences are known for the genus of ribosome inactivating proteins. Applicant does not point to a consensus sequence for the genus of ribosome inactivating proteins.

The examiner respectfully submits that the creation of the resistant cell lines is required; and that it is unclear that cells of interest useful for practicing the full scope of claimed invention in fact exist.

The examiner respectfully submits that resistant cells are first required to practice the claimed invention.

9. Claims 1-7, 9-16, 18, 20, 27-29, 32, 33, 37-41 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of for making a cytotoxic mutant protein or pool of Shiga toxin or Shiga-like toxin proteins, does not reasonably provide enablement for making mutants for any heteromeric ribosome inactivating protein with a different receptor binding specificity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection is necessitated by applicant's amendments to the claims.

This rejection is maintained for the reasons of record as set forth in the previous Office action in the rejection of claims 1-7, 9-16, 42 and 43. That rejection is copied below for the convenience of the reader. The new grounds of rejection are in response to the examination of previously withdrawn claims.

There are many factors be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether undue experiment is necessitated. These factors can include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the relative skill of those in the art;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1 and 2) The breadth of the claims and the nature of the invention: The claims are drawn to a method for making a cytotoxic mutant protein that is a ribosome inactivating protein,(RIP), having a receptor-binding specificity that is different from the specificity of the wild type RIP, comprising incorporating mutations into DNA encoding the binding domain of a heteromeric RIP toxin to produce variant forms of the heteromeric RIP toxin, generating a library of clones to produce variant forms of the heteromeric RIP toxin, screening against a population of screening cells and selecting a cytotoxic mutant protein that inhibits or kills said population of screening cells to a greater extent than wild-type cytotoxic mutant protein. Thus the claim is broadly drawn to making mutants of any heteromeric RIP toxin. The specification at p. 25, , lines 25-29, states that the "B subunit variants may thus bind to a spectrum of molecular entities such as proteins, peptides, nucleic acids or even organic moieties rather than to sugars

or glycolipids (such as CD77)." Therefore, the different receptor to which the variant forms of the mutated cytotoxic protein can bind, is contemplated by the specification to encompass virtually any biological molecule.

(3 and 5) The amount of direction provided by the inventor and the existence of working examples: Applicants have only exemplified the preparation of mutant Shiga toxin, although the example probably is applicable to Shiga-like Toxin-1, as the specification at p. 12, lines 16-19 teaches that both toxins recognize the glycolipid CD77 (also known as Gb_3). In Example 4, pp. 22-23, the specification provides specific embodiments, working or otherwise, only for method used for producing a cytotoxic mutant protein of Shiga-toxin. However, in regard to the embodied species of Shiga-toxin, the specification does not describe what different receptor the mutated B subunit now has specificity for and describes no assays, actual or prophetic, to demonstrate positively that the mutated toxins now have specificity for a different receptor, as claimed. The specification does not disclose the molecule, if any, to which the mutated B subunit of the variant Shiga toxin protein now binds. Also, the specification does not disclose that the mutated B subunits do not bind to the CD77; rather that the mutated toxin kills CAMA-1 cells, which the specification teaches lacks CD77, and SKBR-3 cells, which the specification teaches expresses CD77 (Specification at p. 22, lines 4-14). The specification does not provide guidance or direction for cell lines resistant to RIP other than Shiga toxin or Shiga-like toxin.

Furthermore, in regard to newly examined claims, drawn to methods of making probes and mendicants, the specification does not provide guidance and direction for detecting or treating disease, *in vivo*.

(4) The state of the prior art and the level of predictability in the art Methods for making for making mutant Shiga toxin and mutant Shiga-like toxin was known in the art at the time of filing, however, the correlation of RIP receptor specificity to RIP-induced cytotoxicity is unpredictable. The publication of Battelli, Mini Reviews in Medicinal Chemistry (2004) Vol. 4, pp. 513-521, throughout the publication, and e.g., at p. 513, bridging paragraph and p. 513, para 2, teaches that "[c]omparing the cytotoxicity of various type 2 RIP for a cell line and, conversely, the different sensitivity of various cell lines to the same toxin, it appeared clear that the interaction between cells and RIP was more complicated that it was predictable on the basis of the molecular structure." Battelli states that "t]he correlation between RIP structure and cytotoxicity had become even less linear when a new category of type 2 RIP emerged, which, in spite of the presence of the lectinic chain, have a low toxicity, similar to that of type 1 RIP (Table 1). . . . For instance, the lower cytotoxicity of nigrin b compared with ricin has been at least in part explained by a higher degradation of nigrin b by cells, with a resulting lower concentration remaining inside the cells, and by the different intracellular pathways followed by the two lectins". Thus it is clear that the genus of RIPs is heterogeneous, unpredictable, and complicated in the mechanism of action. Applicant's claimed scope of any heteromeric RIP toxin, such that mutations thereto that result in changed receptor specificity from that of wild type toxin, and such that a population of screening

cells would be killed or inhibited to a greater degree, than by the wild type toxin, represent only an invitation to experiment with the genus of RIP (see also above concerning written description and references and cases cited therein). In view of the uncertainty in the art, extrapolation from cytotoxicity data (see Specification at Example 4, pp. 22-23) that a mutated RIP has a different receptor-binding specificity is unpredictable.

In regard to newly examined claims, drawn to methods of making probes and mendicants, the specification does not provide guidance and direction for detecting or treating of any disease is unpredictable.

In regard to said methods of making mendicants, it is respectfully noted that the instant claims read upon vectors for gene therapy, which is an unpredictable art. In particular, sufficient delivery to and expression in target tissues is not predictable. Kaneda, "Gene Therapy: A Battle Against Biological Barriers", Current Molecular Medicine 2001, Vol. 1, pp. 493-499, throughout the publication and abstract, teaches that successful gene therapy is dependent on the development of an effective gene delivery system. Kaneda teaches that gene therapy continues to stymied by problems in targeting, permanence and quantity of expression of the gene in question, immunogenicity, etc. Kaneda notes that various gene delivery systems, including adenovirus systems, have well known limitations that have prevented safe and successful methods of gene therapy.

(6-7) The level of one or ordinary skill: The level of skill would be high, most likely at the Ph.D. level. However, such persons of ordinary skill in this art, *given its*

unpredictability, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The claims contain only broad recitations of "heteromeric protein toxin that is a ribosome inactivation protein" and mutant variant protein toxins having "a different receptor-binding specificity". However, the instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in carrying out the full scope of the claimed methods. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 and n.23, 20 USPQ2d 1438, 1455 and n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure, undue experimentation would be required of one of ordinary skill in the art to practice the full scope of the claimed invention.

Response to Arguments, mailed 11/20/2006

Applicant argues that the examiner has not stated why one of skill in the art would require undue experimentation to make mutations of any heteromeric RIP toxin. Applicant argues that because the claims require no recognition of the nature of the different receptor, there is no explanation of why this breadth has anything to do with undue experimentation. Applicant argues that the examiner has not provided a reason

why undue experimentation would be required for any of the steps of the claimed invention.

Applicant's arguments entered, 6/27/2006, have been fully considered but they are not persuasive.

As set forth in the previous Office action, undue experimentation would be required of one of skill in the art because the instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in carrying out the full scope of the claimed methods. The specification does not provide guidance and direction for the full scope of making cytotoxic mutant proteins for any heteromeric ribosome inactivating protein toxin because the specification does not provide the nucleic acid sequences for ribosome inactivating proteins and does not provide cell lines that are insensitive to ribosome inactivating protein toxins, except for Shiga toxin and Shiga-like toxin. Furthermore, the specification does not point to where in the prior art, at the time of filing (1998), these gene sequences and cell lines could be found. Therefore, the specification as filed does not provide guidance and direction as to whether the sequences for the heteromeric ribosome inactivating proteins were known; and the practitioner would not be provided guidance and direction for employing cell lines insensitive to the heteromeric ribosome inactivating proteins in the claimed method. Absent evidence to the contrary, one of skill in the art would have to create these elements, before the claimed method could be made and used in its full scope. However, the specification as filed does not provide guidance and direction for the obtaining of the gene sequences or

the making of appropriately insensitive cell lines. Thus the claimed invention does not merely require routine screening, but would require undue experimentation to make and use.

The nature of the receptor is relevant to enablement of the claimed invention, at least because the amended claim states that the mutated proteins have a "receptor-binding specificity for a receptor that is different from the receptor to which the wild type protein has receptor binding specificity". Without recognition of the nature of the receptor to which the mutated protein binds, it is not clear that the receptor is different, as required by the claims. It is noted that one of skill in the art would appreciate that insensitivity to a toxin might result from a variety of reasons, such as amplification of the gene of a target protein or an enhanced toxin efflux mechanism in the insensitive cell, (*compare*, D'Andrea, U.S. 2003/0188326, at para 71, discussing various possible causes for drug resistance).

Because these elements are required to practice the claimed method, their absence would require undue experimentation for one of skill in the art.

Response to Arguments

Applicant argues that the examiner does not indicate why a practitioner would have difficulty practicing the claimed invention. Applicant argues that amendments to claim 1 clarify that because target cells are initially insensitive, therefore the receptor binding specificity must have changed. Applicant argues that the claimed method of making mendicants does not require the use of gene therapy to work. Applicant argues

that the claimed method actually enables gene therapy, by addressing the problem of targeting.

Applicant's arguments, entered 4/9/2007, have been fully considered but they are not persuasive. The examiner respectfully submits that it would be unpredictable to produce insensitive cells to any ribosome inactivating protein toxin. The examiner respectfully argues that it is possible for insensitive cells to become resistant, even though the receptor binding specificity remains the same. The examiner respectfully submits that claims must be given their broadest reasonable interpretation, consistent with the specification, so that the claimed method of making mendicants encompasses gene therapy. The examiner respectfully submits that it is unclear that claimed method enables gene therapy.

Conclusion

10. Claims 1-7, 9-16, 18, 20, 27-29, 32, 33, 37-41 and 43 are rejected.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Shibuya, whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. J. Douglas Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner
Art Unit 1639